UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WISCONSIN

INNOGENETICS, N.V.,

Plaintiff,

vs. Civil Action No. 05-C-0575-C

ABBOTT LABORATORIES,

Defendant.

SUPPLEMENT TO EXPERT REPORT OF BRUCE K. PATTERSON, M.D. REGARDING THE INVALIDITY OF INNOGENETICS, N.V.'S U.S. PATENT NO. 5,846,704

The attached supplemental report is provided pursuant to Rule 26(a)(2)(B), Fed. R. Civ. P. and the Court's Preliminary Pretrial Conference Order in this action. The report includes or incorporates by reference:

1. a signed, complete statement of all supplemental opinions to be expressed by Bruce K. Patterson, M.D. and the bases and reasons therefor;

2. the data and other information considered by Dr. Patterson in forming his opinions;

3. any exhibits to be used as a summary of and/or support for his opinion;

4. Dr. Patterson's qualifications, including a list of all publications he authored in the preceding ten years;

5. the compensation to be paid for Dr. Patterson's study and testimony; and

6. a listing of other cases in which Dr. Patterson testified as an expert within the preceding four years.

SUPPLEMENTAL EXPERT REPORT OF DR. BRUCE PATTERSON

I am submitting this supplement to my opinion of April 10, 2006, to address minor corrections, clarifications, and oversights that I believe should be disclosed in order to render a full and complete opinion. I incorporate by reference my prior report, except as corrected herein.

A. Proper Citation to Kanai, et al.

My April 10, 2006 report on p. 22 contains a discussion of an article by Koichi Kanai and colleagues. My April 10 report mistakenly cited a 1990 article by Kanai that also appeared in the *Lancet*. The correct citation is to an article that appeared *The Lancet* Vol. 339, p. 1543, June 1992, a copy of which is attached to this supplement as Exhibit A.

B. The Cha PCT Application

My April 10, 2006 report on pages 11 and 15 states that the Cha PCT application discloses a genotyping analysis using probes SEQ ID NOs. 77 and 78 to target the 5'-UT region in a genotype-specific manner. As I noted in my report, these probe sequences are listed on p. 36 of the Cha PCT application, along with their nucleotide position using Cha's nomenclature. To avoid any confusion about the nucleotide position of these probes using the nomenclature of the '704 patent, this is established by reference to FIGS. 2 and 4 of the '704 patent, which shows that probe SEQ ID NOs. 77 targets the nucleotides from -137 to -116 of the 5'-UT region, and that probe SEQ ID NO. 78 targets the nucleotides from -171 to -154 of the 5'-UT region.

Given these nucleotide positions, the "genotyping analysis" taught on pages 36-38 of the Cha PCT application discloses Claim 2 of the '704 patent, which recites using two probes simultaneously in the domain extending from -291 to -66 of the 5'-UT region. Both probes 77 and 78 target this domain. It is my understanding that these probes were used simultaneously, because the claim recites that "[i]n another experiment," both probes SEQ ID NOs. 77 and 78 were used. Confirming that these probes were used simultaneously, the Cha application explained on p. 22 that such nucleic acid probes "can be used … in combination with other

nucleic acid probes to detect substantially all genotypes of HCV." Furthermore, given the nucleotide position of SEQ ID NO. 77, section (g) of claim 3 is also taught by the Cha PCT application, because probe SEQ ID NO. 77 hybridizes to at least 5 contiguous nucleotides from the domain extending from position -141 to -117.

With respect to claims 6 and 7, Sequence ID No. 77 of the Cha PCT application corresponds to SEQ ID NO. 24 of the '704 patent (listed for "HCV type 2"). Similarly Sequence ID NO. 78 of the Cha PCT application corresponds to Seq. ID NO. 13 of '704 Patent (listed for "HCV type 3"). Therefore, the use of probes SEQ ID NOs. 77 and 78 as taught on pages 36-38 of the Cha PCT application falls within the method of claims 6 and 7 of the '704 patent.

C. United States Patent 5,580,718 (the "'718 Patent")

In my April 10, 2006 report, on pages 19-21, I state that the Resnick '718 patent disclosed and taught many of the claimed methods of the '704 patent. In particular, I noted that SEQ ID NO. 8 of the Resnick patent corresponds to the 5'-UT region, in that it targets the domain from -244 to -221 of the 5'-UT region.

The probe that I discussed was also used simultaneously with probe SEQ ID NO. 9, as set forth in Example 5 of the Resnick '718 patent. See Resnick '718 Patent, col. 27, lines 57-61. The nucleotide positions of SEQ ID NO. 9 are -136 to -116, as confirmed by comparing the nucleotide sequence of Probe SEQ ID NO. 9 to the HCV domain shown on Figure 4 of the '704 patent. The simultaneous use of these probes discloses the methods in claims 1 and 2 of the '704 patent. Resnick's SEQ ID NO. 8 discloses "at least five contiguous nucleotides in" the domains of claim 3 (d), (e) and (f) of the '704 patent. See '718, col. 133, lines 9-31. Resnick's SEQ ID NO. 9 similarly discloses "at least five nucleotides in" the domains of claim 3 (g) and (j). See id.

I explained in my report on page 20 that the Resnick '718 patent teaches the use of particular primers for carrying out a PCR reaction. I listed primers KY80 (SEQ ID NO. 5) and KY86 (SEQ ID NO. 13), which bind to the domains listed in claim 9 of the '704 patent. See

Resnick '718 Patent, col. 9, lines 19-24. As set forth in Example 5 of the'718 patent, Resnick teaches using KY80 (SEQ ID NO. 5) as an "upstream" primer and KY78 (SEQ ID NO. 18) as a "downstream" primer. Resnick discloses another downstream primer, KY145 (SEQ ID NO. 19) in Table 2 (col. 9). I have compared these sequences to publicly available HCV sequence databases, and confirmed that Resnick's primers SEQ ID NO. 5 hybridizes to the domain from -274 to -251, SEQ ID NO. 18 hybridizes to the domain from -54 to -31, and SEQ ID NO. 19 hybridizes to the domain from -54 to -29, respectively, in the 5'-UT region as numbered in the '704 patent.[1] Resnick's description of these primers for genotyping discloses every element of claim 9.

The experiment performed in Example 5 of the Resnick patent (col. 27, lines 57-61) discloses the methods of claims 1, 2, 3 and 9 of the '704 patent. This is because the probes have the corresponding nucleotide positions to the domains listed in claims 1, 2 and 3, the probes are used simultaneously (as in claim 2), and the primers fall in the correct regions as specified by claim 9.

Dated: 5/17/06

By: _____
Bruce K. Patterson, M.D.

[1] SEQ ID NO. 19 also corresponds exactly with the reverse complement of sequence "No. 4" listed on col. 45 of Innogenetics' '704 patent, which confirms that this probe hybridizes to "Position -29 of 5' end."

EXHIBIT A

experience with intensive CPR-basic life support (BLS) training for more than 2500 people in the area covered by our mobile intensive care unit (MICU), training was given mainly to physicians, nurses, and paramedical personnel. In addition, our 78 anaesthesists have considerable experience in prehospital emergency medicine. To illustrate the importance of body weight we report a female doctor weighing only 40 kg, and with 20 years' experience as an anaesthetist and emergency physician. We found that despite her perfect mastery of CPR-BLS technique she could not attain the prescribed impression depth on the mannequin.

According to the new recommendations of the American Heart Association (AHA) (class I recommendation to the Consensus Conference of the AHA, submitted by the National Conference on Cardiopulmonary Resuscitation and Emergency Cardiac Care in Dallas/Texas, February, 1992) the breathing interval is to be lengthened from 1·5 to 2·0 s, to reduce the risk of gastric distention resulting from too hasty mouth-to-mouth ventilation. Thus the combined time for two ventilations will be roughly 5–6 s. So 5·4 s as breathing interval for two ventilations is correct.

We agree that sufficient time should be set aside during CPR courses for practical exercises. However, we believe that 2 min is too short a time for a test under simulated real-life conditions. For the past six months or so we have been assigning to each participant his own training mannequin (ACTAR 911, Actar Air Force, Toronto) and CPR has been done simultaneously by all participants at least twice during the course for 10 min each time, according to a frequency established by the instructor. Correction of mistakes and more detailed instruction are done with expensive mannequins (Laerdal Resusci Anne, Asmund Laerdal, Stavanger, Norway; also Ambu-Man, Ambu International A/S, Copenhagen, Denmark) costing between eight and fourteen times as much as ACTAR 911, but which much more closely simulate human physiology.

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Is immunotherapy justified for recurrent spontaneous abortion?

SIR,—Despite careful gynaecological examination to exclude anatomical malformations and microbiological, endocrinological, or genetic factors, a cause for recurrent spontaneous abortion (RSA) often cannot be found. It is thought that immunological factors are involved in couples who have had three or more unexplained pregnancy losses in the first trimester. However, spontaneous abortion caused by maternal immune rejection has never been demonstrated in man. Nevertheless, it has been proposed that allogeneically induced effects are required for the maintenance of pregnancy, and that these effects are absent in patients with RSA but can be stimulated by transfusion/vaccination of the mother with allogeneic leucocytes. Controlled studies have produced differing overall success rates for such treatment.[1]

Commercially available, intravenous immunoglobulin (IVIG) processed from a large pool of donors inhibits immune phagocytosis.[2] In uncontrolled trials, maternal IVIG treatment during pregnancy yields results comparable with leucocyte vaccination/transfusion in cases of RSA.[3,4] The mechanism of the possible antiabortive effect of IVIG, however, remains speculative. Immune modulation could be due to passively transferred "blocking" antibodies, idiotypic/anti-idiotypic antibodies influencing the immune network, blockade of macrophage Fc receptors, and/or enhancement of suppressor T-cell function.

Because of the conflicting results of different trials, immunotherapy remains an unvalidated way of preventing RSA. In addition, psychological factors affect pregnancy outcome in couples with RSA.[5] These considerations and the possible side-effects of immunotherapy (eg, allogeneic leucocyte vaccination carries the risk of transmitting infectious diseases and immunisation against MHC antigens) should be carefully weighed against the anticipated effects since no life-saving indication exists in RSA, unlike most situations where the transfusion of blood products or the infusion of immunoglobulin is contemplated.

Because of the uncertainties, we propose that immunotherapy to prevent unexplained RSA should be given only in the context of controlled studies in specialised centres.

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HCV genotypes in chronic hepatitis C and response to interferon

SIR,—Hepatitis C virus (HCV) genomes have been categorised into subtypes[1] which may be related to disease severity.[2] In a trial of interferon-α therapy in chronic hepatitis C, 96 Japanese patients with biopsy-proven hepatitis were enrolled. They all had HCV RNA in their serum by polymerase chain amplification.[3] The dose was 6 MU recombinant IFN-α_{2A} (Nippon Roche) subcutaneously for 7 consecutive days, then 3 MU three times a week for 23 weeks.

HCV genotype[1] frequencies were type II 72%, type III 22%, and type IV 6% (type I was not found). By the 24th week of treatment HCV RNA levels were much decreased in type III patients and became undetectable in 14 (67%). Only 14 (20%) patients with type II and 2 of 6 with type IV responded:

	*HCV RNA**	
HCV genotype	*Before IFN*	*At week 24*
II (n = 69)	+5·2 (1·2)	+2·7 (2·0)†
III (n = 21)	+4·7 (1·1)	+0·8 (1·3)†
IV (n = 6)	+4·8 (1·6)	+3·3 (2·8)

*+1, +2, +3 . . . correspond to 10^4, 10^5, 10^6 . . . cIU/ml.
†$p < 0·001$ (Wilcoxon test). Type II *vs* type III clearance rates (see text) also significant ($p < 0·001$).

HCV genotype seems to be an important factor in determining response to IFN in patients with chronic hepatitis.

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